ORIGINAL ARTICLE

Efficacy of Adjuvant Chemotherapy With Tegafur-Uracil in Patients With Completely Resected, Node-Negative NSCLC—Real-World Data in the Era of Molecularly Targeted Agents and Immunotherapy

Takehito Shukuya, MD, PhD,[a,*] Kazuya Takamochi, MD, PhD,[b] Hiroyuki Sakurai, MD, PhD,[c] Kiyotaka Yoh, MD,[d] Tomoyuki Hishida, MD, PhD,[e] Masahiro Tsuboi, MD, PhD,[f] Yasushi Goto, MD, PhD,[g] Yujin Kudo, MD, PhD,[h] Yasuhisa Ohde, MD, PhD,[i] Sakae Okumura, MD,[j] Masataka Taguri, PhD,[k,l] Hideo Kunitoh, MD[m]

[a]*Department of Respiratory Medicine, Graduate School of Medicine, Juntendo University, Tokyo, Japan*
[b]*Department of General Thoracic Surgery, Graduate School of Medicine, Juntendo University, Tokyo, Japan*
[c]*Division of Respiratory Surgery, Nihon University School of Medicine, Tokyo, Japan*
[d]*Department of Thoracic Oncology, National Cancer Center Hospital East, Kashiwa, Japan*
[e]*Division of Thoracic Surgery, Department of Surgery, Keio University School of Medicine, Tokyo, Japan*
[f]*Division of Thoracic Surgery & Oncology, National Cancer Center Hospital East, Kashiwa, Japan*
[g]*Department of Thoracic Oncology, National Cancer Center Hospital, Tokyo, Japan*
[h]*Department of Surgery, Tokyo Medical University, Tokyo, Japan*
[i]*Division of Thoracic Surgery, Shizuoka Cancer Center, Nagaizumi, Japan*
[j]*Department of Thoracic Surgical Oncology, The Cancer Institute Hospital of JFCR, Tokyo, Japan*
[k]*Yokohama City University School of Data Science, Yokohama, Japan*
[l]*Department of Health Data Science, Tokyo Medical University, Tokyo, Japan*
[m]*Department of Medical Oncology, Japanese Red Cross Medical Center, Tokyo, Japan*

Received 9 January 2022; revised 15 March 2022; accepted 28 March 2022
Available online - 6 April 2022

ABSTRACT

Introduction: In Japan, adjuvant tegafur-uracil (UFT) chemotherapy is recommended for patients with completely resected, stage I NSCLC. This treatment requires real-world re-evaluation because of recent advances in target-based and immuno-oncological treatments and refinement of lung cancer staging.

Methods: The Japan Clinical Oncology Group (JCOG) 0707, a phase 3 trial comparing the benefits of UFT and S-1 (tegafur-gimeracil-oteracil) in patients with completely

*Corresponding author.

Disclosure: Dr. Shukuya received grants from AstraZeneca, Chugai Pharmaceutical, Boehringer Ingelheim, Novartis, and Merck Sharp & Dohme and honoraria from AstraZeneca, Chugai Pharmaceutical, Boehringer Ingelheim, Novartis, Merck Sharp & Dohme, Taiho Pharma, Daiichi Sankyo, Ono Pharmaceutical, Bristol-Myers Squibb, Nippon Kayaku, and Pfizer outside of the submitted work. Yoh received grants from AstraZeneca, Lilly, Pfizer, Daiichi Sankyo, AbbVie, Taiho, Merck Sharp & Dohme, and Takeda and honoraria from AstraZeneca, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Janssen, Eli Lilly, Taiho, Novartis, Kyowa Kirin, and Boehringer Ingelheim outside of the submitted work. Hishida received support for the present work from Taiho Pharmaceutical Company; grants from Covidien Japan, Johnson and Johnson Medical Company, Taiho Pharmaceutical Company, Eli Lilly and Company, and Astellas; and honoraria from Johnson and Johnson Medical Company and AstraZeneca outside of the submitted work. Dr. Tsuboi received grants from Boehringer Ingelheim Japan, Merck Sharp & Dohme, AstraZeneca KK, Ono Pharmaceutical Co., Ltd., Bristol-Myers Squibb KK, Eli Lilly Japan, and Novartis, and honoraria from AstraZeneca, Bristol-Myers Squibb, Chugai, Daiichi Sankyo, Janssen, Lilly, Taiho, Novartis, Kyowa Kirin, and Boehringer Ingelheim outside of the submitted work. Goto received grants from AZK, Pfizer, AbbVie, Eli Lilly, Pfizer, Bristol-Myers Squibb, Ono, Novartis, Kyorin, Daiichi Sankyo, Novartis, and Preferred Networks and fees for speaker's bureaus or advisory board from Eli Lilly, Chugai, Taiho, Boehringer Ingelheim, Bristol-Myers Squibb, Pfizer, Merck Sharp & Dohme, Novartis, Merck, Thermo Fisher, AstraZeneca, Taiho, Guardant Health Inc., Illumina, Daiichi Sankyo, and Ono Pharmaceutical outside of the submitted work. Kunitoh received honoraria from Taiho, Covidien Japan, Merck Sharp & Dohme, EA Pharma, Daiichi Sankyo, Johnson and Johnson, Boehringer Ingelheim, Eisai, AstraZeneca, and Chugai Pharma outside of the submitted work. The remaining authors declare no conflict of interest.

Address for correspondence: Takehito Shukuya, MD, PhD, Department of Respiratory Medicine, Graduate School of Medicine, Juntendo University, 2-1-1 Hongo, Bunkyo-ku, Tokyo 113-8421 Japan. E-mail: tshukuya@juntendo.ac.jp

Cite this article as: Shukuya T, Takamochi K, Sakurai H, et al. Efficacy of adjuvant chemotherapy with tegafur-uracil in patients with completely resected, node-negative NSCLC—real-world data in the era of molecularly targeted agents and immunotherapy. *JTO Clin Res Rep*. 2022;3:100320.

ISSN: 2666-3643

https://doi.org/10.1016/j.jtocrr.2022.100320

resected stage I NSCLC (T1 >2 cm and T2 in the TNM sixth edition), was conducted in Japan. A multicenter observational cohort study (Comprehensive Support Project for Oncology Research [CSPOR]-LC03) was also conducted for those patients excluded from JCOG 0707 during the study enrollment period. Physicians from institutions that participated in JCOG 0707 retrospectively assessed the medical records of each patient. The efficacy of UFT was evaluated in the CSPOR-LC03 cohort.

Results: In the entire study population (n = 5005), patients treated with UFT (n = 1549) had significantly longer overall survival (OS) than those without any adjuvant chemotherapy (n = 3338). There was no significant difference in OS between the patients treated with UFT (n = 1061) and those without adjuvant chemotherapy (n = 1484) in the JCOG 0707-eligible population (logrank $p = 0.755$). For tumors without ground-glass attenuation and size greater than 3 cm, patients treated with UFT had significantly longer survival than those without adjuvant chemotherapy, on univariate but not on multivariate analysis.

Conclusions: There was no significant difference in OS between the patients treated with UFT and those without adjuvant chemotherapy in the clinical trial-eligible population. Adjuvant UFT for patients with completely resected NSCLC may be recommended only in patients with a tumor without ground-glass attenuation and size greater than 3 cm. In patients with node-negative early NSCLC, further study is needed to select patients who will benefit from adjuvant chemotherapy.

Keywords: Non–small cell lung cancer; Adjuvant chemotherapy; Randomized clinical trial; Real-world study; Tegafur-uracil

Introduction

NSCLC accounts for approximately 85% of all lung cancers. Surgery is still considered the principal treatment option in patients with early stage NSCLC, but even these patients have a high risk of recurrence and death from lung cancer.[1] The Japanese nationwide lung cancer registry report analyzed the clinical outcomes of 11,663 patients who underwent surgery in 2004 and revealed that the 5-year overall survival (OS) rate was 85.9% for pathologic stage (p-stage) IA (T1N0M0, T ≤ 3 cm) and 69.3% for stage IB (T2N0M0, T > 3 cm) (TNM sixth edition).[2] According to this report, the OS for the entire p-stage IA group seemed excellent, but the 5-year OS rate for p-stage IA group with a tumor size greater than 2 cm (2.1–3.0 cm) at 69% was unsatisfactory, as was the OS rate for the p-stage IB group.[2]

Cisplatin-based adjuvant chemotherapy has become a global standard of care for patients with completely resected NSCLC, particularly for those with lymph node-positive stages II and III disease.[3] In 2004, a Japanese phase 3 trial revealed that adjuvant chemotherapy with oral tegafur-uracil (UFT) significantly improved OS in comparison with surgery alone for patients with completely resected stage I lung adenocarcinoma, particularly for those with stage IB disease (TNM fifth edition).[4] Furthermore, a meta-analysis of 2003 patients with completely resected NSCLCs from six randomized trials in Japan revealed the efficacy of adjuvant UFT, regardless of the histologic type, and even patients with stage IA disease with T1 greater than 2 cm displayed an absolute 5-year survival benefit of 6%.[5,6] On the basis of these results, adjuvant UFT is generally recommended in Japan for patients with completely resected stage I (T1 > 2 cm and T2 in the TNM fifth edition) NSCLC. Clinical trials have also been conducted to investigate efficacy of adjuvant gemcitabine and carboplatin plus paclitaxel compared with UFT in resected NSCLC, but they could not reveal superiority to UFT.[7,8] Nevertheless, this strategy has not been evaluated in Western populations.

The Japan Clinical Oncology Group (JCOG) conducted a randomized phase III trial (JCOG 0707, registered in the UMIN Clinical Trials Registry as UMIN000001494) comparing the survival benefit of UFT and S-1, a second-generation oral anticancer agent based on UFT, for patients with completely resected p-stage I (T1 > 2 cm and T2 in the TNM fifth edition) NSCLC.[9] Between November 2008 and December 2013, a total of 963 patients were enrolled into this study, which confirmed a favorable survival outcome in patients with completely resected stage I NSCLC treated with UFT.[9]

Although the JCOG 0707 trial reconfirmed a favorable outcome in p-stage I patients treated by adjuvant UFT, there is growing concern that the patients in randomized clinical trials (RCTs) are highly selected and unrepresentative of the real-world population. RCT results would thus not apply to the general patient population.[10] Real-world studies, such as those based on patient registries and observational cohort studies, are required to confirm the results with certainty.

In addition, the Japanese phase 3 trials that revealed OS benefit with oral UFT adjuvant chemotherapy in stage I NSCLC were conducted before 2000. Since then, molecularly targeted agents have been developed against driver oncogenes such as *EGFR* mutations and ALK rearrangements, including anti–programmed cell death protein-1 or programmed death-ligand 1 immunotherapy. These agents can affect postrecurrence survival. Diagnostic modalities have also improved, with

introduction of fluorodeoxyglucose-positron emission tomography for lung cancer staging, and stage migration could also offset the effect of adjuvant UFT.

In lung cancer, TNM staging has traditionally been based on total tumor size. In the past decade, however, data accumulated to support the concept that invasive tumor size was a better predictor of survival than was total tumor size in lung adenocarcinoma, characterized by pathologically invasive tumor components revealing themselves as radiologically solid tumor parts.[11–20] Prognosis can be predicted more reliably after adjusting the T descriptor according to the invasive size in adenocarcinomas with lepidic components on pathologic examination, which correspond to radiologically subsolid (ground-glass) appearance by computed tomography (CT). Hence, T categories for subsolid and assessment part-solid tumors were changed in the eighth edition of the TNM classification of lung cancer.[21] Therefore, we hypothesized that patients with larger invasive tumor size on pathologic examination (solid components on chest CT), which has a higher T-factor in the new classification, may potentially derive more benefit from UFT than other patients.

Herein, a multicenter observational cohort study, Comprehensive Support Project for Oncology Research (CSPOR) LC-03, was conducted on patients excluded from the JCOG 0707 during the study enrollment period. We evaluated the efficacy of UFT after introduction of molecularly targeted agents and immunotherapy in real-world settings. In addition, we sought to evaluate the efficacy of UFT, not according to the size of the tumor, but based on extent of pathologic invasion reflected in the changes in the TNM classification of lung cancer.

Materials and Methods

Study Design

CSPOR LC-03 was conducted to enroll patients who had completely resected p-stage I (T1 $>$ 2 cm and T2 in the TNM fifth edition) NSCLC, as confirmed on lobectomy or pneumonectomy and nodal dissection or sampling, that is, those who belonged to the target population of the JCOG 0707 trial but were excluded during that study's enrollment period. The study was registered in the UMIN Clinical Trials Registry as UMIN000015732. Investigators at the institutions participating in the JCOG 0707 trial recorded data from the medical records of each patient in this study.[22]

In this study, we compared the outcome of patients treated with UFT to that of patients not receiving adjuvant chemotherapy (including UFT) in the entire study population. Next, we focused on the outcomes of the following patients: (1) patients who met the criteria for JCOG 0707, but were not enrolled in the study, receiving UFT in daily clinical practice and (2) patients who met the criteria for JCOG 0707 but did not receive adjuvant chemotherapy including UFT. We compared the outcome of patients treated with UFT with that of the patients without adjuvant chemotherapy including UFT in the aforementioned two groups. The study was conducted in accordance with principles that have their origin in the Declaration of Helsinki and was approved by the institutional review board of each participating institute and the ethics committee at the Public Health Research Foundation. The opt-out method, which provides potential candidates with opportunities to decline to participate through information disclosure by means of posting and publication, was applied to obtain informed consent. This policy is based on the Ethical Guidelines for Epidemiological Research in Japan. Nevertheless, each institution responded by following the instructions from their respective institutional review boards and obtained informed consent from individual patients when those boards deemed it necessary.

Outcome

The primary outcome was OS. We analyzed OS to evaluate the efficacy of UFT. We performed a subgroup analysis in terms of age, histological type, and the appearance of the tumor on high-resolution CT and pathologic examination. The existence of a ground-glass area (GGA) on high-resolution CT, pathologic total tumor size, and pathologic invasive component size were collected regarding the T category. Patients were classified according to the appearance of the tumor on high-resolution CT and pathologic examination into the following five groups: (1) patients with tumor with GGA (GGA+) and tumor size less than or equal to 3 cm; (2) patients with GGA+, tumor size greater than 3 cm, and less than or equal to 3 cm pathologic invasive component size; (3) patients with GGA+, tumor size greater than 3 cm, and greater than 3 cm pathologic invasive component size; (4) patients with tumor without GGA (GGA−), namely, of the pure-solid type, and tumor size less than or equal to 3 cm; and (5) patients without GGA and tumor size greater than 3 cm. GGA− tumors presented as a "pure-solid" type on CT scan and comprised only invasive cancers on pathologic examination.[19] We determined that pathologic invasive component size equals tumor size when the tumor lacked a GGA component on chest CT. Groups 1, 2, and 4 correspond to T1, whereas groups 3 and 5 correspond to T2 to 4 in the eighth edition of the TNM classification of lung cancer.[21]

Causes of death were also analyzed for competing risk assessment as an exploratory analysis.

Statistical Analysis

Patient backgrounds were compared using a chi-square test. The Kaplan−Meier method was used to

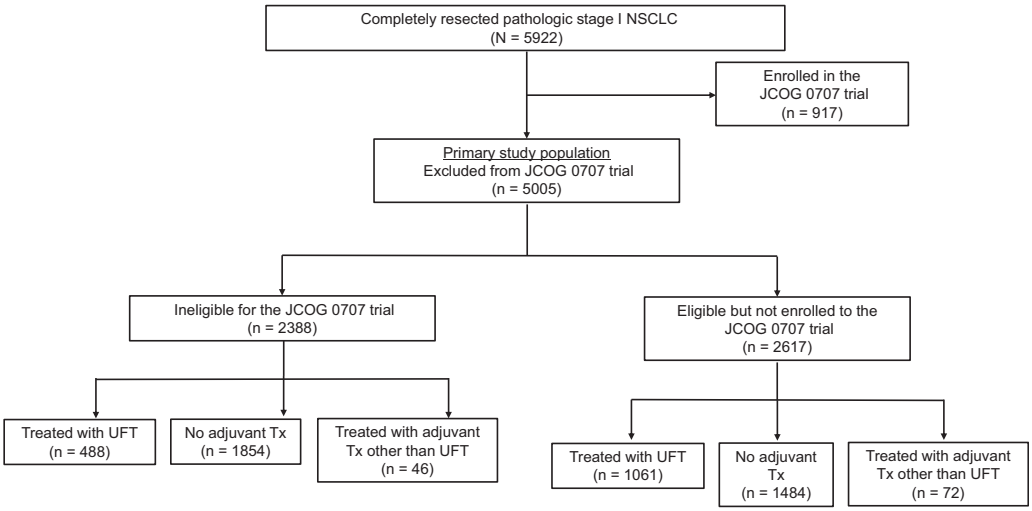

Figure 1. Flowchart describing participants in this study. JCOG, Japan Clinical Oncology Group; Tx, treatment; UFT, tegafur-uracil.

estimate OS curves. The log-rank test was used to evaluate differences in OS among the subgroups. Univariate and multivariate Cox proportional hazards models were used to estimate hazard ratios (HRs) for efficacy of UFT and their 95% confidence intervals (CIs). We also conducted inverse probability of treatment weighted analysis using propensity scores. The potential confounding factors for estimating the propensity scores were as follows: age ($<$70 y or $\geq$70 y), sex (male or female), lymph node dissection (systematic or lobe specific), histological type (adenocarcinoma or non-adenocarcinoma), tumor size (continuous), and pathologic T stage (T1 or $\geq$T2). For the inverse probability of treatment weighted analyses, the SEs were estimated using the robust sandwich variance estimator. As exploratory analyses, we applied cause-specific Cox proportional hazards models for NSCLC deaths and deaths due to other causes, respectively, in patients accrued to CSPOR LC03. Missing data were not imputed. Two-sided p values less than 0.05 were considered statistically significant. All data analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC).

Results

Patient Background

Of the 48 institutions that participated in the JCOG 0707 trial, 34 (enrolling 917, or 95% of all 963 patients registered in the JCOG 0707 trial) cooperated in CSPOR LC-03. A total of 5005 patients with completely resected p-stage I (T1 $>$ 2 cm and T2 in the TNM sixth edition) NSCLC were enrolled in the observational study after being excluded from the JCOG 0707 trial. Figure 1 is a flowchart that describes participants in this study.

Patient characteristics are listed in Table 1. Their median age was 69 years (range: 20–93), and fewer than half of them were women. Most patients had adenocarcinoma on histological type (75%), and the tumor staging classification included 2536 T1 ($>$2 cm) and 2470 T2 tumors. Table 2 reveals the characteristics of the following three groups of patients: (1) patients who met the criteria for JCOG 0707, but were not enrolled in the study, and received UFT in daily clinical practice; (2) patients who met the criteria for JCOG 0707, but did not receive any adjuvant chemotherapy including UFT; and (3) patients who were enrolled in JCOG 0707 and received UFT for reference.[9] There were statistically significant differences in terms of age, sex, lymph node dissection, tumor size, TNM stage, and existence of GGA among the three groups, and there was no significant difference in terms of *EGFR* mutation status.

OS

Figure 2*A* illustrates the Kaplan–Meier curve for OS of the patients treated with UFT (n = 1549) and those without any adjuvant chemotherapy (n = 3338) in the entire study population. Those who received adjuvant treatment other than UFT, such as platinum-based chemotherapy or radiotherapy, were excluded from the analysis. There was a significant difference in OS, favoring those who received UFT. Nevertheless, this may well be a result of selection bias, with those who were fit enough to receive adjuvant therapy treated with UFT, especially in the JCOG 0707 trial-ineligible cohort.

Figure 2*B* illustrates the Kaplan–Meier curve for OS of patients treated with UFT (n = 1061) and those without any adjuvant chemotherapy (n = 1484) in the JCOG 0707-eligible population. There was no significant

Table 1. Patient Characteristics

Characteristics	CSPOR LC-03		
	All N (%)	Eligible for JCOG 0707 but not enrolled n (%)	Ineligible for JCOG 0707 n (%)
No. of patients	5005	2617 (52)	2388 (48)
Age (y)			
<70	2517 (50)	1556 (59)	961 (40)
70-79	2098 (42)	1020 (39)	1078 (45)
>80	390 (8)	41 (2)	349 (15)
Sex			
Female	2089 (42)	1215 (46)	874 (37)
Male	2916 (58)	1402 (54)	1514 (63)
Surgical procedure			
Lobectomy	4982 (99)	2607 (99)	2375 (99)
Pneumonectomy	23 (<1)	10 (<1)	13 (<1)
Lymph node dissection			
Systematic	2276 (45)	1235 (47)	1041 (44)
Lobe specific	2729 (55)	1382 (53)	1347 (56)
Histological type			
Adenocarcinoma	3761 (75)	2084 (80)	1677 (70)
Nonadenocarcinoma	1244 (25)	533 (20)	711 (30)
Tumor size			
<3 cm	2746 (55)	1510 (58)	1236 (52)
≥3 cm	2259 (45)	1107 (42)	1152 (48)
Pathologic TNM (sixth edition)			
T1 (>2 cm)	2536 (51)	1390 (58)	1146 (48)
T2	2469 (49)	1227 (42)	1242 (52)
EGFR mutation status			
Mutant	831 (17)	451 (17)	380 (16)
Wild type	1341 (27)	636 (24)	705 (30)
Unknown	2833 (56)	1530 (59)	1303 (54)
Adjuvant therapy			
None	3338 (67)	1484 (57)	1854 (78)
UFT	1549 (31)	1061 (41)	488 (20)
S-1	21 (<1)	9 (<1)	12 (<1)
Platinum-based chemotherapy	67 (1)	55 (2)	12 (<1)
Others	30 (<1)	8 (<1)	22 (1)

CSPOR, Comprehensive Support Project for Oncology Research; JCOG, Japan Clinical Oncology Group; No., number; UFT, tegafur-uracil.

difference in OS between these groups (logrank $p = 0.755$). Patients in the "JCOG 0707-eligible" cohort were then classified into five groups according to tumor appearance on high-resolution CT. Figure 3 illustrates the Kaplan–Meier curves for OS of the patients treated with UFT and those without any adjuvant chemotherapy according to appearance of the tumor on high-resolution CT. Owing to missing imaging or pathologic information, 26 of 1484 patients without any adjuvant chemotherapy and 28 of 1061 patients treated with UFT could not be grouped according to appearance of the tumor on high-resolution CT. Among patients with a tumor larger than 3 cm without GGA, those treated with UFT had significantly longer survival than those without adjuvant chemotherapy.

Table 3 illustrates subgroup analyses of the effect of UFT on OS according to age, *EGFR* mutation status, histological type, tumor size, and UFT treatment duration in the JCOG 0707 eligible population. As found in Figure 3, on univariate analysis, the patients treated with UFT had significantly longer survival than those without any adjuvant chemotherapy, provided the tumor size was larger than 3 cm and GGA was absent. Nevertheless, no factor was significantly associated with UFT efficacy on multivariate analysis.

OS was significantly different among patients with *EGFR*-mutant and wild-type genes in the JCOG 0707-eligible cohort on univariate analysis, but not on multivariate analysis (*EGFR* mutant or wild type, HR = 0.533, 95% CI: 0.440–0.645, $p < 0.0001$ on univariate analysis and HR = 0.834, 95% CI: 0.667–1.043, $p = 0.1123$ on multivariate analysis), probably reflecting differences in background factors, including sex and smoking history. There was no significant interaction

Table 2. Characteristics of Patients Who Met the Eligibility Criteria of the JCOG 0707 Trial

Factors	JCOG 0707 UFT Treated (n = 462)	CSPOR LC-03 Eligible forJCOG 0707 UFT Treated (n = 1061)	CSPOR LC-03 Eligible forJCOG 0707 No Adjuvant (n = 1484)	*p* Value χ^2 Test
Age (y), n (%)				<0.0001
<70	313 (67.7)	706 (66.5)	797 (53.7)	
70-79	149 (32.3)	351 (33.1)	650 (43.8)	
>80	0 (0.0)	4 (0.4)	37 (2.5)	
Sex, n (%)				0.0427
Female	266 (57.6)	587 (55.3)	767 (51.7)	
Male	196(42.4)	474 (44.7)	717 (48.3)	
Surgical procedure, n (%)				0.2981
Pneumonectomy	1 (0.2)	2 (0.2)	8 (0.5)	
Lobectomy	461 (99.8)	1059 (99.8)	1476 (99.5)	
Lymph node dissection				<0.0001
ND2a-2, n (%)	254 (55.1)	568 (53.5)	613 (41.3)	
ND2a-1, n (%)	207 (44.9)	493 (46.5)	871 (58.7)	
Unknown	1	0	0	
Histological type, n (%)				0.0597
Adenocarcinoma	371 (80.3)	878 (82.8)	1172 (79.0)	
Nonadenocarcinoma	91 (19.7)	183 (17.2)	312 (21.0)	
Tumor size, n (%)				<0.0001
<3 cm	213 (46.1)	437 (41.2)	897 (60.4)	
≥3 cm	249 (53.9)	624 (58.8)	587 (39.6)	
Pathologic TNM (sixth edition), n (%)				<0.0001
T1 (>2 cm)	223 (48.3)	377 (35.5)	872 (58.8)	
T2	239 (51.7)	684 (64.5)	612 (41.2)	
EGFR mutation status				0.5178
Mutant, n (%)	-	191 (40.9)	250 (42.9)	
Wild type, n (%)	-	276 (59.1)	333 (57.1)	
Unknown	-	594	901	
GGA				0.0005
+, n (%)	-	441 (41.8)	718 (48.8)	
−, n (%)	-	615 (58.2)	754 (51.2)	
Unknown	-	0	0	

CSPOR, Comprehensive Support Project for Oncology Research; GGA, ground-glass attenuation; JCOG, Japan Clinical Oncology Group; UFT, tegafur-uracil.

between UFT effect and *EGFR* mutation status (Table 3).

In exploratory analyses of causes of deaths in patients accrued to CSPOR LC03, those without adjuvant chemotherapy had a higher risk of death owing to causes other than the original NSCLC, when compared with those with UFT, both in the JCOG 0707-eligible and JCOG 0707-ineligible cohorts (Supplementary Table 1*A* and *B*).

Discussion

This study is one of the largest observational studies to investigate survival benefits of adjuvant

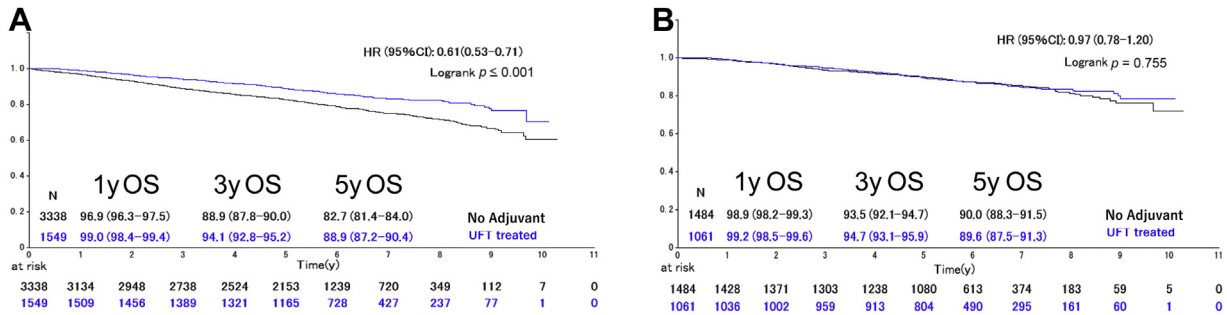

Figure 2. (*A*) Kaplan-Meier curve of OS of patients treated with UFT (n = 1549) and those without adjuvant chemotherapy, including UFT (n = 3338), for the entire study population. (*B*) Kaplan-Meier curve of OS of patients treated with UFT (n = 1061) and those without adjuvant chemotherapy, including UFT (n = 1484), in the JCOG 0707-eligible population. CI, confidence interval; HR, hazard ratio; JCOG, Japan Clinical Oncology Group; OS, overall survival; UFT, tegafur-uracil; y, year.

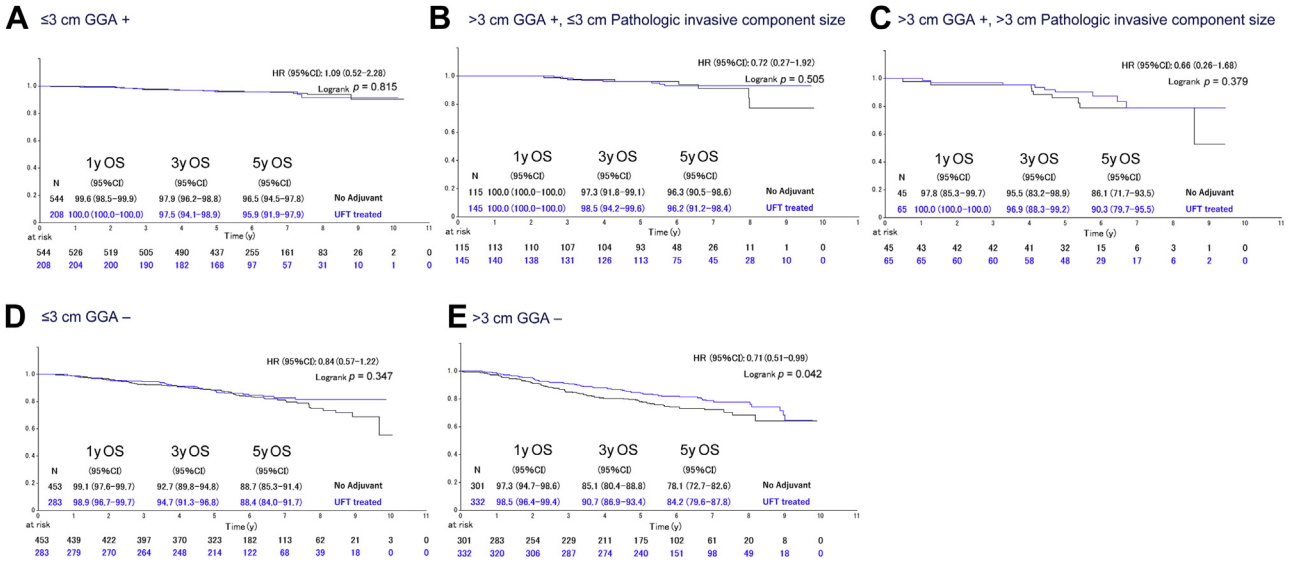

Figure 3. Kaplan-Meier curves of OS of patients treated with UFT and those without UFT treatment, on the basis of the appearance of the tumor on high-resolution CT. CI, confidence interval; CT, computed tomography; GGA, ground-glass area; HR, hazard ratio; JCOG, Japan Clinical Oncology Group; OS, overall survival; UFT, tegafur-uracil; y, year.

chemotherapy in patients with completely resected, node-negative NSCLC. As described in our previous study, just 15% of patients with completely resected early stage NSCLC in Japan were enrolled in the JCOG 0707 clinical trial for adjuvant chemotherapy, during the enrollment period.[22] One-third of the patients excluded from the JCOG 0707 trial received adjuvant chemotherapy, most of them with UFT. In general, the implementation of adjuvant chemotherapy for completely resected NSCLC is reported to be low, with 22% to 40% of patients in clinical practice receiving adjuvant chemotherapy.[23–26]

Unfortunately, this observational study could not reproduce the survival benefit of UFT found in previous prospective clinical trials and meta-analyses.[4–6] Although the outcomes of those who received adjuvant UFT were better than those with surgery alone, this might reflect selection bias, with "fit" patients more likely to receive adjuvant UFT. The observation that those without any adjuvant therapy had a higher risk of death due to causes other than the original NSCLC strongly suggests the presence of such bias. In fact, the benefit of UFT was not apparent in the clinical trial-eligible cohort. Therefore, we tried to explore which population might benefit from UFT, by focusing on this "trial-eligible" population.

The T categories for subsolid nodules and assessment of tumor size in part-solid tumors were changed in the eighth edition of the TNM classification of lung cancer.[21] Therefore, we evaluated the efficacy of UFT not according to the size of the tumor, but the pathologic invasive component size. On univariate analysis, patients treated with UFT had significantly longer survival than those without adjuvant chemotherapy, provided the tumor size was larger than 3 cm and GGA was absent. Therefore, adjuvant UFT for patients with completely resected NSCLC may be recommended only in this population, although this survival benefit is not significant on multivariate analysis. In the Japanese phase 3 study evaluating efficacy of UFT in patients with completely resected stage I lung adenocarcinoma (TNM fifth edition), the Kaplan−Meier OS curves for the UFT arm and surgery-alone arm separated significantly after seven years, and the follow-up time in the current study might not be sufficient to detect a significant difference in OS between patients treated with UFT and those without adjuvant chemotherapy. As chemotherapy using molecularly targeted agents and immunotherapy have improved, it is likely that these changes might also have affected postrecurrence survival and masked the effect of UFT.

The safety and efficacy outcomes of eligible and ineligible patients for the SWOG leukemia trials were found to be comparable in a recent report.[27] We suggest that the study eligibility criteria for RCTs should reflect the real-world population as much as possible without affecting on the primary end point (such as OS).[28,29] Real-world data are becoming more important as some anticancer agents have been approved using real-world data.[30] Nevertheless, when considering the biases of clinical studies, data from RCTs are more reliable than retrospective real-world data. We should be careful in adopting data from retrospective, real-world studies into

Table 3. Subgroup Analyses of the Effect of UFT on Overall Survival According to Age, *EGFR* Mutation Status, Histological type, Tumor Size, and UFT Treatment Duration

	Univariate Analysis				Multivariate Analysis				IPTW Method			
		95% CI				95% CI			HR	95% CI		
Subgroup	HR	Lower	Upper	*p* Value	HR	Lower	Upper	*p* Value		Lower	Upper	*p* Value
All patients	0.9661	0.7776	1.2003	0.7554	0.8926	0.7108	1.1210	0.3285	0.9294	0.7371	1.1719	0.5360
EGFR mutation												
EGFR mutant	1.1571	0.7049	1.8995	0.5639	0.8745	0.5153	1.4839	0.6191	1.0139	0.6011	1.7101	0.9587
EGFR wild	0.8530	0.5989	1.2148	0.3781	0.8332	0.5720	1.2138	0.3419	0.7826	0.5345	1.1456	0.2074
CT appearance, pathologic tumor size and invasive tumor size												
GGA+, tumor size ≤3 cm	1.0919	0.5220	2.2840	0.8154	0.9893	0.4584	2.1351	0.9781	1.0023	0.4697	2.1390	0.9952
GGA+, tumor size >3 cm, Pathologic invasive component size ≤3 cm	0.7167	0.2577	1.9934	0.5233	0.5330	0.1800	1.5786	0.2560	0.7255	0.2584	2.0370	0.5424
GGA+, tumor size >3 cm, Pathologic invasive component size >3 cm	0.6607	0.2693	1.6212	0.3655	0.8345	0.3117	2.2342	0.7189	0.8064	0.3199	2.0329	0.6484
GGA−, tumor size ≤3 cm	0.8352	0.5731	1.2172	0.3487	0.9786	0.6626	1.4453	0.9133	0.8779	0.5854	1.3167	0.5290
GGA−, tumor size >3 cm	0.7070	0.5067	0.9866	0.0414	0.8316	0.5846	1.1829	0.3050	0.7723	0.5482	1.0881	0.1396
Adeno, GGA+, tumor size ≤ 3 cm	1.1630	0.5534	2.4445	0.6902	1.0744	0.4985	2.3154	0.8547	1.0713	0.4998	2.2960	0.8595
Adeno, GGA+, tumor size > 3 cm, pathologic invasive component size ≤3 cm	0.7287	0.2425	2.1894	0.5728	0.7358	0.2463	2.1979	0.5826	1.0713	0.4998	2.2960	0.8595
Adeno, GGA+, tumor size >3 cm, pathologic invasive component size >3 cm	0.4736	0.1679	1.3358	0.1577	0.6059	0.1948	1.8846	0.3868	0.7330	0.2409	2.2306	0.5844
Adeno, GGA−, tumor size ≤3 cm	0.7702	0.4801	1.2356	0.2789	0.8554	0.5249	1.3940	0.5307	0.5383	0.1852	1.5650	0.2554
Adeno, GGA−, tumor size >3 cm	0.7381	0.4700	1.1591	0.1872	0.8401	0.5241	1.3465	0.4691	0.7803	0.4696	1.2966	0.3384
Age												
<70 y old	0.9077	0.6644	1.2402	0.5432	0.8133	0.5876	1.1256	0.2127	0.8768	0.6304	1.2196	0.4349
≥70 y old	1.1942	0.8726	1.6342	0.2677	0.9579	0.6909	1.3280	0.7963	0.9739	0.7037	1.3478	0.8734
Histological type												
Adenocarcinoma	1.0531	0.8075	1.3734	0.7027	0.8928	0.6740	1.1825	0.4290	0.9384	0.7090	1.2419	0.6564
Other than adenocarcinoma	0.9002	0.6140	1.3199	0.5904	0.9016	0.6071	1.3390	0.6079	0.8802	0.5846	1.3253	0.5412
Duration of UFT treatment												
Duration <3 mo	1.2774	0.9210	1.7717	0.1425	1.2824	0.9229	1.7821	0.1384	1.2786	0.8932	1.8302	0.1793
3 mo ≤ duration <6 mo	2.3277	1.6329	3.3182	<0.0001	2.1754	1.5227	3.1077	<0.0001	2.4933	1.7129	3.6292	<0.0001
6 mo ≤ duration	0.5607	0.4207	0.7473	0.0001	0.5143	0.3808	0.6946	<0.0001	0.5526	0.4027	0.7582	0.0002

Adeno, adenocarcinoma; CI, confidence interval; CT, computed tomography; GGA, ground-glass attenuation; HR, hazard ratio; IPTW, inverse probability of treatment weighted; UFT, tegafur-uracil.

clinical practice and interpret them together with the data from other studies, including RCTs.

Major limitations of our study are as follows. There were no data for relapse-free survival (RFS). The observational study in which the 34 institutions participated was retrospective, and the data on RFS were unreliable for use in analysis. RFS is now a useful end point, as postrecurrence survival is improving owing to introduction of molecularly targeted agents and immunotherapy. Other data from the observational study are retrospective as well and are not as accurate as those from prospective clinical trials. In addition, we could not retrieve data on postrecurrence therapy, which undoubtedly contributed to OS. The lack of a significant OS benefit in this study could also be attributed to deaths owing to causes other than lung cancer. As the prognosis of node-negative patients with NSCLC is improved, such competing events make up a more substantial portion of deaths, even in populations registered in clinical trials.[9] We believe that improvement of chemotherapy including molecularly targeted agents and immunotherapy might have affected postrecurrence survival and masked an effect of UFT in this study, but we could not directly find it because we did not collect the data of subsequent therapies. As we described in the introduction, clinical trials of adjuvant UFT have been conducted, and its use is recommended only in Japan. Nevertheless, clinical trials which revealed benefit of adjuvant cisplatin-based chemotherapy were conducted in similar era, early 2000, as well. Therefore, real-world data of this study can be extrapolated in patients who received adjuvant cisplatin-based chemotherapy outside of Japan.

In conclusion, patients treated with UFT had significantly longer survival than patients without adjuvant chemotherapy in the subgroup with a tumor larger than 3 cm and no GGA, in this real-world study. Although this survival benefit is not significant on multivariate analysis, the duration of follow-up might have been insufficient to detect any benefit of adjuvant UFT. As chemotherapy has improved, including molecularly targeted agents and immunotherapy, these changes might have affected postrecurrence survival and masked an effect of UFT in this study. Further study is needed to select patients who will benefit from adjuvant chemotherapy among those with node-negative, early NSCLC with patient background, image finding, pathologic finding, or biomarker.

CRediT Authorship Contribution Statement

Takehito Shukuya, Kazuya Takamochi: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Writing - original draft.

Hiroyuki Sakurai, Kiyotaka Yoh, Tomoyuki Hishida, Masahiro Tsuboi: Conceptualization, Investigation, Methodology, Resources, Writing - review & editing.

Yasushi Goto: Conceptualization, Investigation, Methodology, Resources, Writing - original draft.

Yujin Kudo, Yasuhisa Ohde, Sakae Okumura: Resources, Writing - review & editing.

Masataka Taguri: Data curation, Formal analysis, Resources, Writing - original draft.

Hideo Kunitoh: Conceptualization, Formal analysis, Investigation, Methodology, Resources, Writing - original draft, Supervision, Project administration, Funding acquisition.

Acknowledgments

This work was supported by funding from Taiho Pharmaceutical under a study contract. The Comprehensive Support Project for Oncology Research of the Public Health Research Foundation in Japan conducted this study. Taiho Pharmaceutical had no role in the design of the study. The company did not participate in the collection, management, analysis, or interpretation of the data; the preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication. The authors thank all 34 institutions that participated in this multicenter study conducted in Japan.

Supplementary Data

Note: To access the supplementary material accompanying this article, visit the online version of the *JTO Clinical and Research Reports* at www.jtocrr.org and at https://doi.org/10.1016/j.jtocrr.2022.100320.

References

1. Goldstraw P, Crowley J, Chansky K, et al. The IASLC Lung Cancer Staging Project: proposals for the revision of the TNM stage groupings in the forthcoming (seventh) edition of the TNM classification of malignant tumours. *J Thorac Oncol*. 2007;2:706–714.
2. Sawabata N, Miyaoka E, Asamura H, et al. Japanese lung cancer registry study of 11,663 surgical cases in 2004: demographic and prognosis changes over decade. *J Thorac Oncol*. 2011;6:1229–1235.
3. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. *J Clin Oncol*. 2008;26:3552–3559.
4. Kato H, Ichinose Y, Ohta M, et al. A randomized trial of adjuvant chemotherapy with uracil-tegafur for adenocarcinoma of the lung. *N Engl J Med*. 2004;350:1713–1721.
5. Hamada C, Tanaka F, Ohta M, et al. Meta-analysis of postoperative adjuvant chemotherapy with tegafur-uracil in non-small-cell lung cancer. *J Clin Oncol*. 2005;23:4999–5006.

6. Hamada C, Tsuboi M, Ohta M, et al. Effect of postoperative adjuvant chemotherapy with tegafur-uracil on survival in patients with stage IA non-small cell lung cancer: an exploratory analysis from a meta-analysis of six randomized controlled trials. *J Thorac Oncol*. 2009;4:1511–1516.
7. Toyooka S, Okumura N, Nakamura H, et al. A multicenter randomized controlled study of paclitaxel plus carboplatin versus oral uracil-tegafur as the adjuvant chemotherapy in resected non-small cell lung cancer. *J Thorac Oncol*. 2018;13:699–706.
8. Yamaguchi M, Tada H, Mitsudomi T, et al. Phase III study of adjuvant gemcitabine compared with adjuvant uracil-tegafur in patients with completely resected pathological stage IB-IIIA non-small cell lung cancer (WJTOG0101). *Int J Clin Oncol*. 2021;26:2216–2223.
9. Kunitoh H, Tsuboi M, Wakabayashi M, et al. A phase III study of adjuvant chemotherapy in patients with completely resected, node-negative non-small cell lung cancer (JCOG 0707). *JTCVS Open*. 2020;4:90–102.
10. de Lusignan S, Crawford L, Munro N. Creating and using real-world evidence to answer questions about clinical effectiveness. *J Innov Health Inform*. 2015;22:368–373.
11. Yoshizawa A, Motoi N, Riely GJ, et al. Impact of proposed IASLC/ATS/ERS classification of lung adenocarcinoma: prognostic subgroups and implications for further revision of staging based on analysis of 514 stage I cases. *Mod Pathol*. 2011;24:653–664.
12. Warth A, Muley T, Meister M, et al. The novel histologic International Association for the Study of Lung Cancer/American Thoracic Society/European Respiratory Society classification system of lung adenocarcinoma is a stage-independent predictor of survival. *J Clin Oncol*. 2012;30:1438–1446.
13. Tsutani Y, Miyata Y, Mimae T, et al. The prognostic role of pathologic invasive component size, excluding lepidic growth, in stage I lung adenocarcinoma. *J Thorac Cardiovasc Surg*. 2013;146:580–585.
14. Maeyashiki T, Suzuki K, Hattori A, Matsunaga T, Takamochi K, Oh S. The size of consolidation on thin-section computed tomography is a better predictor of survival than the maximum tumour dimension in resectable lung cancer. *Eur J Cardiothorac Surg*. 2013;43:915–918.
15. Matsunaga T, Suzuki K, Hattori A, et al. Lung cancer with scattered consolidation: detection of new independent radiological category of peripheral lung cancer on thin-section computed tomography. *Interact Cardiovasc Thorac Surg*. 2013;16:445–449.
16. Suzuki K, Koike T, Asakawa T, et al. A prospective radiological study of thin-section computed tomography to predict pathological noninvasiveness in peripheral clinical IA lung cancer (Japan Clinical Oncology Group 0201). *J Thorac Oncol*. 2011;6:751–756.
17. Tsutani Y, Miyata Y, Nakayama H, et al. Prognostic significance of using solid versus whole tumor size on high-resolution computed tomography for predicting pathologic malignant grade of tumors in clinical stage IA lung adenocarcinoma: a multicenter study. *J Thorac Cardiovasc Surg*. 2012;143:607–612.
18. Murakawa T, Konoeda C, Ito T, et al. The ground glass opacity component can be eliminated from the T-factor assessment of lung adenocarcinoma. *Eur J Cardiothorac Surg*. 2013;43:925–932.
19. Hwang EJ, Park CM, Ryu Y, et al. Pulmonary adenocarcinomas appearing as part-solid ground-glass nodules: is measuring solid component size a better prognostic indicator? *Eur Radiol*. 2015;25:558–567.
20. Burt BM, Leung AN, Yanagawa M, et al. Diameter of solid tumor component alone should be used to establish T stage in lung adenocarcinoma. *Ann Surg Oncol*. 2015;22(suppl 3):S1318–S1323.
21. Travis WD, Asamura H, Bankier AA, et al. The IASLC Lung Cancer Staging Project: proposals for coding T categories for subsolid nodules and assessment of tumor size in part-solid tumors in the forthcoming eighth edition of the TNM classification of lung cancer. *J Thorac Oncol*. 2016;11:1204–1223.
22. Yoh K, Takamochi K, Shukuya T, et al. Pattern of care in adjuvant therapy for resected Stage I non-small cell lung cancer: real-world data from Japan. *Jpn J Clin Oncol*. 2019;49:63–68.
23. Williams CD, Gajra A, Ganti AK, Kelley MJ. Use and impact of adjuvant chemotherapy in patients with resected non-small cell lung cancer. *Cancer*. 2014;120:1939–1947.
24. Buck PO, Saverno KR, Miller PJ, Arondekar B, Walker MS. Treatment patterns and health resource utilization among patients diagnosed with early stage resected non-small cell lung cancer at US community oncology practices. *Clin Lung Cancer*. 2015;16:486–495.
25. Salazar MC, Rosen JE, Wang Z, et al. Association of delayed adjuvant chemotherapy with survival after lung cancer surgery. *JAMA Oncol*. 2017;3:610–619.
26. Shukuya T, Takahashi T, Tamiya A, et al. Actual status of adjuvant chemotherapy for non-small-cell lung cancer at one Japanese cancer center: the need for increased cooperation between medical oncologists and surgeons. *Med Oncol*. 2010;27:932–937.
27. Asamura H, Chansky K, Crowley J, et al. The International Association for the Study of Lung Cancer Lung Cancer Staging Project: proposals for the revision of the N descriptors in the forthcoming 8th edition of the TNM classification for lung cancer. *J Thorac Oncol*. 2015;10:1675–1684.
28. Statler A, Othus M, Erba HP, et al. Comparable outcomes of patients eligible versus ineligible for SWOG leukemia studies. *Blood*. 2018;131:2782–2788.
29. Gerber DE, Laccetti AL, Xuan L, Halm EA, Pruitt SL. Impact of prior cancer on eligibility for lung cancer clinical trials. *J Natl Cancer Inst*. 2014;106:dju302.
30. Wedam S, Fashoyin-Aje L, Bloomquist E, et al. FDA approval summary: palbociclib for male patients with metastatic breast cancer. *Clin Cancer Res*. 2020;26:1208–1212.